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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,669	10/01/2003	Kevin P. Baker	10466/485	1088

7590 02/27/2006

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 02/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,669	BAKER ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/24/06*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment of 01 October 2003 has been entered in full.

2. Claims 1-21 are canceled.

3. Claims 22-26 are pending and under examination.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on 24 March 2004 has been fully considered by the examiner. A signed copy of the IDS accompanies this Office Action.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application, by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The oath or declaration has changes to the citizenship of inventor Dan L. Eaton that are non-initialed and non-dated.

Specification

6. The disclosure is objected to because of the following informalities:

a. If applicant desires priority under 35 U.S.C. 119(e), 120, 121 and 365(c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application on the first line of the specification.

For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application. When the domestic benefit of a prior provisional application is being claimed under 35 U.S.C. 119(e), however, the relationship between the two applications should not be specified.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application".

b. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 25, line 10, page 27, line 31, page 94, line 32. Applicant is reminded to check the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

c. The use of trademarks has been noted in this application. For example, see page 95, lines 16, 30, 31, 35-36, page 116, line 5, page 119, line 37 and page 120, lines 1, 7 and 9. Trademarks should be capitalized wherever they appear and be

accompanied by the generic terminology. Applicant is reminded to review the entire disclosure for additional trademarks that require correction.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

d. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Consider the following title: "METHOD FOR DIAGNOSING LUNG AND COLON CANCER USING PRO357 SPECIFIC ANTIBODIES" or similar title that is clearly indicative of the invention to which the claims are directed.

e. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections 35 USC §§ 101 and 112, First Paragraph

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 22-26 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to a method for diagnosing lung or colon cancer comprising contacting a lung or colon tissue sample from a mammalian subject with an antibody that specifically binds to the polypeptide of SEQ ID NO:69 (PRO357), and diagnosing said subject with cancer if the presence of said polypeptide is detected and wherein the antibody is a monoclonal antibody, humanized antibody or is an antibody fragment and wherein the antibody is labeled.

The specification discloses at pp. 13-14 discusses the structure of PRO357, however, the specification does not disclose any secondary or tertiary structural features of this polypeptide (other than a transmembrane domain; see Figure 26). The specification does not disclose any additional information regarding PRO357 such as subcellular localization, timing of regulation during cellular differentiation, which hormones or transcription factors regulate PRO357, or what physiological significance PRO357 plays. Therefore, it is a totally new, uncharacterized polypeptide with no well-established utility.

At pages 125-127 of the specification, it is disclosed that nucleic acids encoding PRO357 had a ΔCt value of at least 1.0 for a number of primary ling and colon tumors. At page 121, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as a quantitative measurement of the

relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results. It is noted that the specification states that samples are used if their values are within 1 Ct of the "normal standard". It is further noted that the ΔCt values are expressed (a) with values to one one-thousandth of a unit (e.g. 1.185), and (b) that very few values were obtained that were at consistently at least 2 (at least on a sample size of 2) (i.e., 5 out of 42 samples; see Table 10). Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO357 genomic DNA shows a positive correlation with lung or colon cancer, much less that the levels of PRO357 genomic DNA would be diagnostic of such. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Furthermore, the literature reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy before the epithelial cells turn cancerous. See Hittelman (2001, Ann. NY Acad. Sci. 952:1-12), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the specification does not provide a direct comparison between the lung tumor samples and normal lung epithelium. Rather, the assay discloses amplification of PRO357 genomic DNA in lung tumors compared to "normal human DNA" (apparently from blood

samples), and thus one skilled in the art would not conclude that PRO357 genomic DNA is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO357 genomic DNA is a diagnostic probe for lung cancer unless it is clear that PRO357 genomic DNA is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Also, while it might be argued in hindsight that PRO357 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is not well-established in the prior art.

Moreover, the data for PRO357 genomic DNA have no bearing on the utility of the claimed PRO357 polypeptide. In order for the PRO357 polypeptide to be overexpressed in lung and colon tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1, gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al.

(Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels could be established for PRO357, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al (2003, Journal of Proteome Research 2(4):405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may

turn out to be important, most are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances, which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 2-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 3-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient" (see Abstract).

Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who

found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291 , abstract). Additionally, Hanish S (Nature Reviews, Applied Proteomics Collection, pp. 9-14, March 2005) states "For example, a gene can be amplified 100-fold in certain tumors with no demonstrable effect on RNA levels for that gene." "Alternatively, protein levels can be increased, decreased or modified with no demonstrable changes in the levels of their corresponding RNAs." (see page 9). Hanash also indicates "no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics" (see abstract). Human tumors are more complex and heterogenous than expected, and are caused by defects in numerous pathways and factors at many levels and incorporation of different genome-scale global profiling are expected to lead to molecular-based classifications of cancer that transcend organ and tissue types and supercede classifications based on the expression patterns of genes with unknown functional significance as in the present case for PRO357.

Therefore, data pertaining to PRO357 genomic DNA do not indicate anything significant regarding the claimed PRO357 polypeptides. The data do not support the assertion that PRO357 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO357 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, and thus, the asserted utility is not substantial. In the absence of information regarding whether or not PRO357 polypeptide levels are also different between specific cancerous and normal tissues, the

proposed use of the PRO357 polypeptide as diagnostic marker is simply a starting point for further research and investigation into potential practical uses of the polypeptide. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "'The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[I]t is not a reward for the search, but compensation for its successful conclusion."

10. Claims 22-26 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

35 U.S.C. § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation "diagnosing said subject with cancer" in claim 22 because the broader limitation "cancer" together with the narrower limitation "diagnosing lung or colon cancer" in the same claim raises confusion over the intended

scope of the claims. It is not clear if the recitation "diagnosing lung or colon cancer" in the preamble of claim 22 is merely exemplary and not required since the presence of the polypeptide (SEQ ID NO:69) is only positively correlated with diagnosing "cancer" in general (last two lines of claim 22). As written, one skilled in the art would not be reasonably apprised of the metes and bounds of the claimed diagnostic method. Amending the last two lines of claim 22 to recite "and diagnosing said subject with lung or colon cancer if the presence of said polypeptide is detected" would overcome this rejection, provided no new matter is introduced.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827